

reducing sugars. This confirms the election made in the telephone discussion with the Examiner on October 22, 1992. With the present response, claims 3-5 are cancelled.

Claims 1, 2, 6-8 and 10-13 stand rejected under 35 USC 112, second paragraph, for being indefinite. These claims are said to recite dicarboxylic acid salts, although among the salts listed, citric acid and isocitric acid are said not to be dicarboxylic acids. The Examiner kindly suggested that Applicants simply use the phrase "salt of the acids."

The Examiner also objected to "delay of a decrease" with reference to the gonadotropin activity as "delay" is a relative expression.

With the present amendments the reference to the acid salts by a dicarboxylic acid salt has been amended to refer to "at least one salt of an organic acid selected from the group consisting of ... ". The dependent claims are amended to conform with the amendment to claim 1 in this regard.

The present amendment change the phrase "to delay a decrease in the gonadotropin's activity" to read ", whereby a decrease in gonadotropin activity over time is delayed." Although no specific time period is defined, as the decrease in activity is a constant matter, which is reduced or delayed using a composition according to the present invention. The "whereby" phrase merely recites the result of providing a composition according to the invention and, it is believed, does not in any

way make the defined composition indefinite because the composition, i.e., its components, are defined.

The Examiner has objected to Applicants' use of the phrase "a second gonadotropin" in claims 7 and 10 for being indefinite. The Examiner asked how this is distinguished from the first.

In order to clear up any misunderstanding, claims 7 and 10 have been amended to recite compositions comprising "more than one type of gonadotropin." The claims are intended to cover compositions comprising any type of gonadotropin. These claims are specifically directed compositions comprising more than one gonadotropin. For example, as discussed in the specification in the first paragraph on page 4, gonadotropins may be FSH LH or HCG. Also, on page 3, the third full paragraph, TSH is mentioned along with the others. The α and β subunits are also intended.

In the fourth full paragraph on page 3 it is discussed that gonadotropins may be obtained from natural sources and may also be synthesized. It is well known in the art that gonadotropins purified from natural sources normally contain gonadotropins of more than one type. For instance, commercial FSH compositions of FSH purified from urine contain a measurable quantity of LH, and perhaps other gonadotropins. In certain procedures combinations of gonadotropins are called for. It is for this reason that more than one gonadotropin is intended to be covered in certain embodiments of the invention. This is not indefinite

as one of ordinary skill knows the different gonadotropins and the fact that they may be found alone or in combination.

The Examiner has noted that the units of ionic strength had not been provided in claim 11. Those units are now introduced with the present amendment.

Claims 1, 2, 6-8 and 10-13 stand rejected under 35 USC 103 for being obvious over Koyama et al. taken in view of Kawaguchi et al., Hamilton et al. and Hayashi et al. Koyama et al. is relied on for teaching stabilized gonadotropin preparations containing an amino acid and a saccharide. The gonadotropin could be a recombinant one. Also the preparation is freeze-dried. Kawaguchi et al. is relied on for teaching lyophilized erythropoietin preparations and the use of combinations of stabilizers, sucrose and citrates. Hamilton et al. is relied on for teaching compositions in a dry state containing growth hormones, non-reducing sugars and citrates. Aspartate and glutamate are disclosed. Hayashi et al. teach freeze-dried preparations of TNF comprising a well known non-reducing sugar and a stabilizer. In view of these, the Examiner concluded that it would have been obvious to one of ordinary skill in the art to include the specific sugars and acids taught by Kawaguchi et al., Hamilton et al. and Hayashi et al. and the generic teachings of Koyama et al. for being components and combinations that are well known stabilizers for sensitive biologically active proteins.

The rejection over Koyama et al. taken in view of Kawaguchi et al., Hamilton et al. and Hayashi et al. is respectfully traversed. Koyama et al. teaches stabilized gonadotropin compositions containing an amino acid and a saccharide. Koyama et al., however, teach the use of polysaccharide stabilizers in their compositions, particularly polysaccharides within the molecular weight range of 20,000 to 2,000,000 daltons (column 2, lines 40-44) which are required to be present. An amino acid and/or a saccharide may be incorporated into the aqueous solution prior to drying. However, the polysaccharide stabilizer must always be there. Koyama et al. do not teach the use of an organic acid salt in stabilization, which is essential to the present invention.

Kawaguchi et al. teach lyophilized erythropoietin preparations using several types of stabilizers, but they do not suggest anything related to lyophilized gonadotropin preparations or their stabilization.

The Examiner's attention is respectfully directed to the statement of Hamilton et al. U.S. Patent 4,816,568, in column 1, line 64 through column 2, line 1:

"While the prior art has taught a number of various stabilizers for specific proteins, unfortunately, the fact a particular stabilizer is effective with a particular protein does not necessarily mean that the particular stabilizer is appropriate for the stabilization of a growth promoting hormone."

There is no reason for concluding that a stabilizer effective for one type of protein, such as erythropoietin (Kawaguchi et

al.) will be effective for stabilizing compositions of gonadotropins as in the present invention.

All of the components recited are critical. For example, the organic acid salts critical to the presently claimed compositions are not taught by Hamilton et al. or any of the references. The gonadotropin preparations of the present invention require specific components for stabilization that are not taught in the prior art, certainly not for use in stabilizing gonadotropins. Hamilton et al. describe dry compositions containing growth hormones that do not use the organic acid salts of the presently claimed compositions, which Applicants have found to be critical for stabilization.

Hayashi et al. teach freeze-dried compositions of tumor necrosis factor (TNF) that do not use acid salts according to the invention for stabilization.

In view of the above the teachings of Koyama et al. taken in view of Kawaguchi et al., Hamilton et al. and Hayashi et al. do not suggest the present invention to one of ordinary skill in the art. They teach other required components but not the use of an organic acid salt for stabilizing purified gonadotropin compositions.

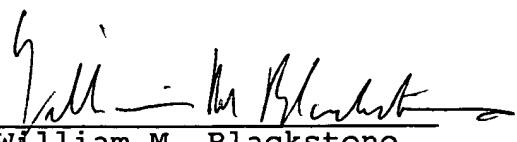
Claims 1, 2, 6-8 and 10-13 stand rejected under 35 USC 103 for being obvious over Koyama et al. taken in view of Kawaguchi et al., Hamilton et al. and Hayashi et al., as well as taken further in view of Fernandes et al., Toray and Yasushi et al.

The rejection over the previously discussed references in combination with Fernandes et al., Toray and Yasushi et al. is respectfully traversed. The rejection is traversed over the previously mentioned prior art for the reasons discussed above. Furthermore, the newly cited references do not provide broad teaching of stabilization using the acid salts according to the claimed composition for stabilizing gonadotropins. Furthermore the process of Fernandes et al. is pasteurization, not lyophilization, and Yasushi et al. do not teach stabilizing compounds. The critical requirement of a carboxylic acid salt for stabilization is not disclosed in any of these references.

In view of the above, with the present amendments, it is believed that Applicants' claims 1, 2, 6-8 and 10-13 are in condition for allowance. Favorable action is solicited.

In the event any fees are required with this paper, please charge our Deposit Account No. 02-2334, for which purpose duplicate copies are enclosed.

Respectfully submitted,



William M. Blackstone
Attorney for Applicants
Registration No. 29,772

AKZO PHARMA
1330-A Piccard Drive
Rockville, Maryland 20850-4373
Tel: (301) 258-5200
WMB:sp

33demeer.amd